Incidence and Impact of CMV Infection in Very Low Birth Weight Infants

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KEY WORDS

cytomegalovirus, very low birth weight, sensorineural hearing loss, neurodevelopmental impairment

ABBREVIATIONS

BPD—bronchopulmonary dysplasia
CI—confidence interval
CMV—cytomegalovirus
GMFCS—Gross Motor Function Classification System
IVH—intraventricular hemorrhage
NDI—neurodevelopmental impairment
NEC—necrotizing enterocolitis
PVL—periventricular leukomalacia
RNICU—Regional Neonatal ICU
SNHL—sensorineural hearing loss
UAB—University of Alabama in Birmingham
VLBW—very low birth weight

Dr Turner was responsible for primary data collection from the UAB Neonatology and Infectious Disease databases, and she participated extensively in the data analysis and manuscript preparation; Dr Lee was responsible for all statistical analyses, and he edited the manuscript; Dr Boppana contributed patient data from the UAB Infectious Disease database, provided technical expertise regarding CMV infection, and edited the manuscript; Dr Carlo contributed patient data from the UAB Neonatology Generic database, provided study design expertise, and edited the manuscript; Dr Randolph conceptualized and designed the study, supervised data collection, and wrote the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Congenital cytomegalovirus (CMV) infection is a leading cause of sensorineural hearing loss and neurodevelopmental impairment in full-term infants. The incidence of congenital CMV infection in preterm infants and the possible associations with developmental outcomes are unknown.

WHAT THIS STUDY ADDS: This study defines the incidence of congenital CMV infection in very low birth weight infants and identifies strong associations of congenital CMV infection with hearing loss and adverse neurodevelopmental outcomes in this population.

abstract

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BACKGROUND AND OBJECTIVES: Congenital cytomegalovirus (CMV) is the leading cause of nongenetic deafness in children in the United States and can cause neurodevelopmental impairment in term infants. Limited data exist regarding congenital CMV infections in preterm infants. We aimed to determine the incidence and association with outcomes of congenital CMV in very low birth weight (VLBW) preterm infants.

METHODS: VLBW infants born in 1993 to 2008 and admitted to the University of Alabama in Birmingham Regional Neonatal ICU were screened on admission for congenital CMV. CMV status and clinical outcomes were identified by using internal patient databases and hospital-based medical records. The primary outcome was death. Secondary outcomes included evidence of neurologic injury in the form of abnormal cranial ultrasound findings, sensorineural hearing loss, or abnormal motor development. Multivariate analysis was performed.

RESULTS: Eighteen of 4594 VLBW infants had congenital CMV (0.39%; 95% confidence interval, 0.25%–0.62%). An additional 16 infants (0.35%; 95% confidence interval, 0.21%–0.57%) were identified who acquired CMV postnatally. Congenital CMV was not associated with death. Compared with controls, congenitally infected VLBW infants were more likely to have hearing loss at initial screening (67% vs 9%, $P < .0001$) and confirmed at follow-up (83% vs 2.1%, $P < .0001$). Congenital CMV was also associated with abnormal neuroimaging (72% vs 25%, $P < .0001$) and adverse developmental motor outcomes (43% vs 9%, $P = .02$). Acquired CMV was not associated with any adverse outcomes.

CONCLUSIONS: Congenital CMV in VLBW infants is associated with high rates of neurologic injury and hearing loss but not death. *Pediatrics* 2014;133:e609–e615

Human cytomegalovirus (CMV) is the most common congenital viral infection in developed countries and is a leading cause neurologic injury, including hearing loss and neurodevelopmental impairment (NDI), in childhood.^{1,2} A member of the herpes virus family, CMV is ubiquitous, infecting >90% of the population by school age in developing countries and 50% to 85% of women of childbearing age in the United States and Europe.³ Transmission from mother to neonate can occur transplacentally, perinatally via cervical or vaginal secretions, or postpartum via breast milk.¹ Congenital infection occurs in 0.5% to 1.5% of US live births, with higher prevalence in African American infants and infants of lower socioeconomic status.^{2,4} The majority of congenital infections are clinically silent, but 10% to 15% are symptomatic and can present with intrauterine growth restriction, petechial rash, microcephaly, intracranial calcifications, chorioretinitis, thrombocytopenia, neutropenia, and hepatosplenomegaly with associated direct hyperbilirubinemia and transaminitis.² Of infected infants who are symptomatic at birth, the majority develop neurologic sequelae, including progressive sensorineural hearing loss (SNHL) and poor neurodevelopmental outcomes.^{4–7} SNHL, sometimes delayed, can also occur in 10% to 15% of congenitally infected infants who are asymptomatic at birth.^{8,9} In contrast, postnatal infection in term infants rarely has significant clinical consequences.² Premature infants who acquire the infection from breast milk can become acutely ill, but more often the infection is clinically silent and carries little risk of long-term sequelae.^{10–15}

Prematurity is another major health burden of infancy. In a recent large study of very low birth weight (VLBW) infants with birth weights of 501 to 1500 g in the United States, mortality rates

were ~13%, and >40% of survivors suffered a major associated morbidity, including sepsis, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), severe intraventricular hemorrhage (IVH), periventricular leukomalacia, and retinopathy of prematurity.¹⁶ Data from the National Institute of Child Health and Human Development Neonatal Research Network hospitals indicate that for surviving infants born at ≤27 weeks' gestation, ~10% will have NDI, and 2% will have hearing loss.¹⁷

Although congenital CMV and prematurity independently contribute to mortality and poor neurologic outcomes, little is known about the simultaneous occurrence of these 2 conditions. Congenital CMV and prematurity might be predicted to interact on a number of levels. CMV is known to infect placental tissues, but it is not known whether CMV-driven placental inflammation commonly triggers preterm labor, resulting in a correspondingly high incidence of congenital infection in preterm infants.¹⁸ CMV-mediated hearing loss might be exacerbated by the ototoxic antibiotics and diuretics frequently used in intensive care. CMV-mediated thrombocytopenia and neutropenia might be expected to increase rates of IVH and sepsis, respectively.

The purpose of this study was to explore the potential interactions of congenital CMV and extreme prematurity. By querying CMV and VLBW databases available at our institution, we determined the rate of congenital CMV infection in VLBW infants. We compared mortality rates, outcomes during admission, and, where available, 18- to 24-month neurodevelopmental outcomes of infected preterm infants with those of uninfected VLBW controls to determine the synergistic effects of congenital CMV and prematurity. We also identified preterm infants who were symptomatic from CMV that was acquired from

breast milk after 2 weeks of age and compared their outcomes with those of additional controls.

METHODS

This was a retrospective study of all inborn or transferred preterm infants with birth weights ≤1500 g cared for in the Regional Neonatal ICU (RNICU) at the University of Alabama in Birmingham (UAB) from January 1993 to December 2008. All infants admitted to the UAB RNICU are screened for congenital CMV by urine or saliva rapid culture within the first 2 weeks of life. This includes infants transferred before 2 weeks of life from outside facilities. Exclusion criteria for this study were gestational age ≥37 weeks, birth weight >1500 g, and death before CMV testing. In infants meeting inclusion criteria, cases of congenital CMV infection were identified through queries of the UAB electronic medical record system (Horizon); the UAB Neonatology Division Database; the UAB Generic Database, which stems from UAB's participation in the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network; the UAB Infectious Disease Division and Diagnostic Virology Laboratory records; and patient paper charts. During the database search, additional infants were identified who were classified as having symptomatic acquired CMV if they were found to have CMV in the urine after 2 weeks of age after a negative CMV screen on admission. Two infants with congenital CMV received ganciclovir; no infants with acquired CMV received ganciclovir or any other antiviral therapy.

We chose control infants from the UAB Generic Database for detailed data collection and analysis by selecting the 10 eligible infants with birth dates closest to those of the CMV cases. This sampling strategy was used rather than matching by gestational age or birth

weight because congenital CMV is a known cause of intrauterine growth restriction and low birth weight and potentially of other clinical factors being studied. All controls were CMV negative at initial screening. For each of the cases and controls, demographic data and outcome data for the admission were extracted from the UAB Generic Database. Demographic data variables extracted included maternal age, highest level of education achieved, and median income of the zip code of residence as a proxy for socioeconomic status. Additional patient characteristics extracted included birth weight, gestational age, gender, and ethnicity. Neurodevelopmental follow-up information, including motor examinations and audiologic evaluations at 18 to 24 months, was also obtained where available. All aspects of this study were approved by the UAB Institutional Review Board.

The primary outcome was death, with secondary outcomes being evidence of neurologic injury in the form of abnormal cranial ultrasound findings, SNHL, or abnormal motor development. Abnormal cranial ultrasound findings included IVH grade ≥ 2 , as defined by Papile's criteria, cystic changes or periventricular leukomalacia (PVL), or calcifications.¹⁹ Suspected SNHL was defined as failure of repeated auditory brainstem response hearing screens in the newborn period. Confirmed SNHL was defined as documented hearing loss at the time of follow-up. Abnormal motor development was defined as a Gross Motor Function Classification System (GMFCS) score of ≥ 3 . Additional outcomes evaluated included respiratory distress syndrome, defined as the need for oxygen for >24 hours, BPD defined as an oxygen requirement at 36 weeks' postmenstrual age, proven NEC of Bell's staging criteria IIA or greater, retinopathy of prematurity of stage ≥ 3 or plus disease in either eye, and culture-proven early- or late-onset sepsis.

Statistical analysis was performed with Stata 11 (Stata Corp, College Station, TX). Categorical variables were compared by using Fisher's exact test. Continuous variables such as birth weight and gestational age were compared by using Student's *t* test. Apgar scores and income were compared by using the Wilcoxon–Mann–Whitney test. A 2-tailed *P* value $<.05$ was designated as indicating statistical significance. For select outcome variables, multivariable logistic regression was used to assess the independent risk impact of CMV infection, controlling for potential confounding factors of maternal age, race, antenatal steroids, gestational age, and small for gestational age status.

RESULTS

Incidence and Demographics of Congenital CMV in Premature Infants

CMV screening was completed, and results were available for $>95\%$ of

infants admitted to the UAB RNICU. Of the 4594 VLBW infants reviewed from January 1993 to December 2008, 18 infants tested positive for congenital CMV, for an incidence of 0.39% (95% confidence interval [CI], 0.25%–0.62%). CMV-positive infants were compared with 180 CMV-negative control infants from the UAB Generic Database. A demographic comparison of infected infants and controls is shown in Table 1. Mothers of infants with congenital CMV were more likely to be <20 years old (50% vs 20%, *P* = .012) and less educated, achieving less than a high school diploma (57% vs 19%, *P* = .024). Although the difference was not statistically significant, most mothers of infants with congenital CMV were African American, compared with approximately half of controls (80% vs 51%, *P* = .09). No significant differences were observed between infants with congenital CMV and controls when we compared rates of maternal receipt of antenatal steroids or antibiotics, mode of delivery, infant gender, mean

TABLE 1 Congenital CMV: Maternal Demographics and Infant Characteristics

	CMV ⁺ (n = 18)	CMV [−] (n = 180)	P
Maternal age, %			
<20 y	50	20	.012
20–29 y	39	50	
30–39 y	6	27	
≥ 40 y	6	2	
Estimated median income ^{a,b}	\$31 800	\$30 700	.93
Education, %			
Less than high school diploma	57	19	.02
High school diploma	43	38	
More than high school diploma	0	43	
Race, %			
Black	80	51	.09
White	20	48	
Other	0	1	
Antenatal steroids given, %	78%	84%	.55
Antibiotics given, %	89%	79%	.54
Vaginal delivery, %	61%	38%	.08
Male infant, %	56%	45%	.46
Mean gestational age, wk	28.7	27.6	.16
Mean birth weight, g	966	970	.96
Small for gestational age, %	33	19	.21
Median Apgar score at 5 min	6	7	.44
Transferred from outside hospital, %	0	5	.60

^a Estimated based on median income of households in maternal zip code.

^b Information was missing for the following variables for some patients: income (*n* = 2), education (*n* = 138), and race (*n* = for 3).

gestational age, mean birth weight, median 5-minute Apgar score, or transfer from an outside hospital.

Outcomes of Preterm Infants With Congenital CMV

Comparisons of outcomes between congenital CMV cases and control infants are shown in Table 2. No significant differences were seen between infants with congenital CMV and controls in the primary outcome of death when death was considered alone or after adjustment for confounding variables. However, congenital CMV was associated with a higher frequency of poor neurologic outcomes. Thirteen of 18 (72%) of the infants with congenital CMV had abnormal neuroimaging, compared with 45 of 180 (25%) of control infants ($P < .001$). Infants with congenital CMV were more likely to develop hearing loss than control infants. At the time of discharge 67% of congenitally infected infants had suspected SNHL, compared with 9% of controls ($P < .0001$). These findings remained when patients transferred from outside facilities were excluded.

For infants for whom 18- to 24-month follow-up data were available, 10 of 12 infected infants had confirmed SNHL, compared with 1 of 47 controls (83% vs 2%, $P < .0001$). Developmental motor outcomes were also significantly worse for infants with congenital CMV, with more infected infants having GMFCS of ≥ 3 (43% vs 9%, $P = .048$), although this information was available for only 7 infants with congenital CMV and 43 control infants.

In a multivariate analysis (Table 3), infants with congenital CMV had an odds ratio of 7.8 for abnormal neuroimaging (95% CI, 2.2–28.1) and 87.6 for suspected hearing loss (95% CI, 11.8–653.4). Because hearing loss and death are potentially competing outcomes, we also looked at the combined outcome of suspected hearing loss and

TABLE 2 Congenital CMV: Infant Outcomes

	CMV ⁺ (n = 18)	CMV ⁻ (n = 180)	P
Death (%)	3/18 (17)	34/180 (19)	1.00
Suspected SNHL ^a (%)	10/15 (67)	12/138 (9)	<.0001
Confirmed SNHL ^b (%)	10/12 (83)	1/47 (2)	<.0001
Neurologic imaging			
Normal or Grade 1 (%)	5/18 (28)	122/180 (68)	<.0001
Grade 2, 3, or 4 (%)	6/18 (33)	31/180 (17)	
Cystic changes or PVL (%)	5/18 (28)	9/180 (5)	
Shunt (%)	0/18 (0)	3/180 (2)	
Calcifications (%)	2/18 (11)	1/180 (1)	
No imaging (%)	0/18 (0)	14/180 (8)	
RDS (%)	12/18 (67)	139/180 (77)	.38
BPD or death (%)	6/18 (33)	66/180 (37)	1.00
Early sepsis (%)	0/18 (0)	0/180 (0)	
Late sepsis (%)	5/18 (28)	40/180 (22)	.56
NEC (%)	3/18 (17)	11/180 (6)	.12
GI perforation (%)	0/18 (0)	7/180 (4)	1.00
ROP (n = 126), (%)	1/13 (8)	10/113 (9)	1.00
GMFCS ≥ 3 , (%)	3/7 (43)	4/43 (9)	.048

GI, gastrointestinal; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity.

^a Failed repeated auditory brainstem response hearing screens at the time of discharge.

^b Documented hearing loss at follow-up.

death. The odds ratio of suspected hearing loss and death for VLBW infants with congenital CMV was 40.6 (95% CI, 7.1–231.1).

Other outcomes were not significantly different between CMV-positive and CMV-negative infants. CMV-positive infants had 3 times the rate of NEC as control infants, but this difference did not reach statistical significance (6% vs 17%, $P = .096$). The frequency of respiratory distress syndrome, BPD, and early- and late-onset sepsis were similar between cases and controls.

Characteristics of Patients With Symptomatic Acquired CMV Infection

Sixteen of the 4594 (0.35%; 95% CI, 0.21%–0.57%) VLBW infants in the study period were diagnosed with symptomatic

acquired CMV with negative initial screening cultures followed by positive urine cultures >2 weeks after birth (Table 4). Screening after 2 weeks was not performed routinely, but rather urine cultures were sent on symptomatic infants for whom the clinical course justified sending a urine culture. Demographic characteristics were similar between infants with acquired CMV and controls, with the exception that infants with acquired CMV were more likely to have been delivered vaginally (75% vs 46%, $P < .034$). Of clinical outcomes, there was a trend toward greater spontaneous gastrointestinal perforation in infants who developed acquired CMV (13% vs 2%, $P = .07$) (Table 5). In contrast to congenital CMV, acquired CMV was not associated with significant neurologic sequelae. Six of 16 (38%) infants with acquired

TABLE 3 Congenital CMV: Adjusted^a Odds Ratios of Outcomes

	Odds Ratio	95% CI
Death	1.2	0.2–9.0
Abnormal neuroimaging	7.8	2.2–28.1
Suspected SNHL ^b	87.6	11.8–653.4
Suspected SNHL and death ^c	40.6	7.1–231.1

^a Adjusted for maternal age and race, antenatal steroids, gestational age, and small for gestational age.

^b n = 148 (excluding deaths and hearing screen results unknown).

^c n = 188 (excluding screening results unknown).

TABLE 4 Acquired CMV: Maternal Demographics and Infant Characteristics

	CMV ⁺ (n = 16)	CMV ⁻ (n = 160)	P
Maternal age, %			
<20 y	13	18	.1
20–29 y	40	60	
30–39 y	47	19	
≥40 y	0	3	
Estimated median income ^{a,b}	\$31 400	\$31 300	.89
Education, %			
Less than high school degree	22	28	.82
High school degree	22	30	
More than high school	56	42	
Race, %			
Black	56	46	.62
White	38	48	
Other	6	6	
Antenatal steroids given, %	88	83	1.00
Antibiotics given, %	81	78	1.00
Vaginal delivery, %	75	46	.03
Male infant, %	38	46	.64
Mean gestational age, wk	27.1	27.8	.31
Mean birth weight, g	922	1005	.26
Small for gestational age, %	6	19	.31
Median Apgar at 5 min	8	7	.32
Transferred from outside hospital, %	6	11	1.00

^a Estimated based on median income of households in maternal zip code.

^b Missing variables for maternal age (n = 1), income (n = 4), education (n = 77), and Apgar score (n = 5).

CMV had abnormal neuroimaging, as compared with 55 of 160 (34%) of CMV-negative infants ($P = .43$). Suspected SNHL was noted in 20% of infants with acquired CMV, compared with 14% of controls ($P = .47$). Developmental motor outcomes, available for 6 infants with acquired CMV, were not significantly different from those in controls.

DISCUSSION

CMV and prematurity are both significant causes of neonatal morbidity and mortality, but the interactions between CMV infections and prematurity remain incompletely understood. Using unique databases from the UAB Divisions of Pediatric Infectious Diseases and Neonatology, we were able to determine the incidence of congenital CMV infection in

VLBW infants at our institution to be 0.39% (95% CI, 0.25%–0.62%). Curiously, this is a lower number than the 0.5% to 1% incidence that has been reported for term infants in our region.^{20,21} The incidence of congenital CMV may be lower in preterm infants because the opportunities for transplacental transmission are cut short by early delivery. The lower-than-expected incidence also may suggest that CMV-mediated placental inflammation does not typically trigger preterm birth.

Although uncommon, congenital CMV infection appears to have significant consequences when it intersects with prematurity, as we observed much higher rates of disability in CMV-positive VLBW infants than are typically seen in either infected term infants or uninfected VLBW infants. In preterm VLBW infants without CMV, estimates of the incidence of hearing loss range from 0.7% to 2%.^{17,22} In term infants with congenital CMV, it is estimated that 17% to 20% of infants will have hearing loss or neurodevelopmental impairment.²³ In the current study, we found that CMV-positive VLBW infants had significantly higher rates of SNHL (83% vs 2%), abnormal neuroimaging (72% vs 25%), and poor motor outcomes (43% vs 9%) when compared with CMV-negative VLBW controls. However, there were no differences between CMV-positive infants and controls in the primary outcome of death.

Recent randomized trials have shown ganciclovir to be effective in reducing long-term hearing loss and NDI in term infants with symptomatic congenital CMV infection with central nervous system involvement.^{24,25} In term infants, the high frequency of asymptomatic infection (~90%) together with the prolonged hospitalization needed for intravenous ganciclovir make the screening and treatment of all term infants with congenital CMV problematic. In preterm infants, our results

TABLE 5 Acquired CMV: Infant Outcomes

	CMV ⁺ (n = 16)	CMV ⁻ (n = 160)	P
Death (%)	1/16 (6)	19/160 (12)	.50
Suspected SNHL (%)	3/15 (20)	18/127 (14)	.47
Neurologic imaging			
Normal or Grade 1 (%)	10/16 (63)	105/160 (66)	.43
Grade 2, 3, or 4 (%)	4/16 (25)	28/160 (18)	
Cystic changes or PVL (%)	1/16 (6)	17/160 (11)	
Shunt (%)	0/16 (0)	6/160 (4)	
Calcifications (%)	1/16 (6)	1/160 (1)	
No imaging (%)	0/16 (0)	3/160 (2)	
RDS (%)	13/16 (81)	118/160 (74)	.76
BPD and death (%)	6/16 (38)	36/160 (23)	.21
Early sepsis (%)	0/16 (0)	5/160 (3)	1.00
Late sepsis (%)	6/16 (38)	29/160 (18)	.09
NEC v	0/16 (0)	7/160 (4)	1.00
GI perforation (%)	2/16 (13)	3/160 (2)	.07
ROP (%)	0/15 (0)	7/112 (6)	.32

GI, gastrointestinal; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity.

suggest that congenital CMV has important neurologic consequences more often than not. Because preterm infants are hospitalized already, antiviral therapy, if tolerated, may be warranted in these patients. However, there are no data on the safety and efficacy of ganciclovir in preterm infants from randomized controlled trials. Two infants with congenital CMV in this study did receive ganciclovir. Both ultimately had hearing deficits, but it is not possible to draw meaningful conclusions about the effectiveness of ganciclovir in preterm infants from such a small sample size.

Consistent with other studies, our results show that acquired CMV is usually without long-term sequelae, even for infants who present with symptomatic infection. The UAB RNICU exclusively uses CMV-negative blood for transfusions, so CMV in these infants was probably acquired through breast milk or vaginal secretions at the time of delivery. Interestingly, a history of vaginal delivery was more common in infants with acquired CMV. An additional finding in the current study is a trend toward a positive association between acquired CMV and isolated gastrointestinal perforation. CMV-related gastrointestinal disease including perforation has been reported previously.^{15,26–28} A larger trial with prospective screening

at regular intervals for acquired CMV would be needed to confirm or refute this potential association, especially because it is possible in our study that infants with gastrointestinal perforation presented with a constellation of symptoms that simply made them more likely to be tested for CMV.

The strengths of this study include the large number of infants studied and the prospective nature of the screening for congenital infection. Important limitations stem from the infrequency of infection. Before the study, based on the reported frequency of congenital CMV infection in term infants of 0.5% to 1%, we estimated that our data set of >4500 infants would yield between 23 and 45 infants to study for long-term outcomes. Instead, we identified only 18 VLBW infants with congenital CMV, even though the screening itself was robust, with >95% of infants in the study period being screened. This limited the power of our study: Only a difference in mortality of >40% would have achieved statistical significance given a baseline mortality rate of 19% in the controls. Thus, although there does not appear to be a significant difference in mortality rates between CMV-positive and CMV-negative infants (6% vs 12%, $P = .5$), our study was underpowered to detect small differences. Similarly, complete

follow-up information was available for only a subset of the 18 infants, so our power to detect associations of CMV with developmental outcomes was further limited. The analysis of infants with acquired CMV was limited by the fact that not all infants were screened for CMV after 2 weeks of age. Rather, CMV testing was performed only for symptomatic infants in whom the health care team suspected a CMV infection; therefore, we could not determine the overall frequency of acquired CMV including asymptomatic infections. In addition, it is possible that rare asymptomatic infants with acquired CMV were incorrectly classified as CMV-negative controls because the controls were not specifically tested for CMV.

In summary, although congenital CMV occurs infrequently in VLBW infants, it is associated with high rates of SNHL and neurodevelopmental impairment. Screening of mothers and VLBW infants at risk and additional studies of the safety and efficacy of antiviral therapy in this high-risk population may be warranted. These would probably have to be large multicenter studies that include long-term neurodevelopmental follow-up, given the low incidence of congenital CMV and the importance of the neurologic sequelae of infection in this population.

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